SHARED CARE PRESCRIBING GUIDELINE

Denosumab (Prolia®) For The Treatment Of Osteoporosis In Post-Menopausal Women And Adult Males (≥ 50 years) At Increased Risk Of Fractures

NOTES to the GP
The expectation is that this shared care guideline should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing this drug.

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills, and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If a GP is happy to accept shared care, they should return the acceptance letter (appendix 3) to the Specialist as soon as possible.

If a GP is not confident or willing to accept shared care, then they should write to the consultant within 14 days, outlining the reasons. NB GPs can contact the specialist team for training and support at any time.

The overall clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

"Shared care" occurs when a secondary care specialist retains a responsibility for the on-going monitoring or review of a patient after the point in time when they consider it clinically appropriate for the patient's General Practitioner (GP) to take over the responsibility of routine prescribing. This usually only applies to long-term treatment with drugs that are not part of most GPs' routine practice.

Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.

Patients will only be referred to the GP once the GP has agreed in each individual case and the hospital will continue to provide prescriptions until successful transfer of responsibilities
The patient's best interests are always paramount.

DENOSUMAB (PROLIA®): - SHARED CARE PRESCRIBING GUIDELINE

This shared care guideline outlines the sharing of responsibilities between secondary care specialists, primary care clinicians (GPs) and the patient/carer where appropriate and covers the use of Denosumab as per the criteria outlined in the BLMK osteoporosis guideline: click here

i.e.

- Management of osteoporosis in post-menopausal women in primary care (both primary and secondary prevention of osteoporotic fragility fractures) (as per NICE - TA 204)
- Management of osteoporosis in men (age ≥ 50 years) in primary care (both primary and secondary prevention of osteoporotic fragility fractures
- Prevention and Treatment of glucocorticoid-induced osteoporosis in post-menopausal women **and** men (age ≥ 50 years) (in primary care)

When can denosumab be considered?
Denosumab can be considered as a treatment option for eligible patients (as per the BLMK osteoporosis guideline) in the following situations:

- **As an alternative to the use of po / IV bisphosphonate if bisphosphonates are contraindicated or not tolerated**

- **As a joint third line treatment option -** Either denosumab s/c or IV zoledronic acid or IV ibandronic acid can be used as a third line treatment option following the use of a first- or second-line oral bisphosphonate.

- **First line treatment choice in patients with severe renal impairment** (as oral and IV bisphosphonates should be avoided in severe renal impairment).
  NB: When denosumab is used in these patients the responsibility for prescribing and monitoring patients should **remain** with secondary care specialists (***Not suitable for shared care – NO GP prescribing).***

Denosumab (Prolia®)
The initial injection of denosumab should be prescribed and administered by a secondary care specialist. If the patient is subsequently stable and free from adverse reactions, care can be transferred to the primary care clinician who may administer the second and subsequent injections at 6 monthly intervals.

Missing an injection by more than 2 weeks (after that 6-month target date) can lead to increased risk of osteoporotic fracture. **Due to the potential reduction in BMD with cessation of denosumab, the dosing frequency of every six months plus or minus two weeks either side, needs to be maintained.** Treatment effect reverses rapidly, so NOT suitable for 'drug holidays' as can be considered for bisphosphonate treatment.

The manufacturer therefore offers a patient-reminder system called Prolong. Details of how patients can register for Prolong support are in the Prolia® packs.

Clinical Information and Monitoring Requirements

Key clinical information and monitoring requirements for denosumab (Prolia®) are included in appendix 1

For MHRA Drug Safety Updates relating to denosumab – see Appendix 2

Individual Responsibilities under Shared Care:

Hospital Specialist Team – At Initiation of therapy

1. To discuss treatment options with the patient and ensure that the patient is suitable for treatment with denosumab according to NICE guideline and local agreement.
2. Carry out baseline blood tests to check renal function and serum adjusted calcium levels and vitamin D levels before starting therapy.
3. Prior to initiating therapy, Secondary care specialist to confirm **absence** of:
    a. **Hypocalcaemia -** must be corrected by ensuring adequate intake of calcium and vitamin D (serum 25-OH vitamin D level of greater than 50nmol/L) before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis or vitamin D deficient are at greater risk of developing hypocalcaemia and, only in these patients, clinical monitoring of calcium levels two weeks after injection is recommended.
    b. **Hypersensitivity** to the active substance or to any of its excipients e.g., fructose
    c. **Pregnancy, lactation**
    d. **Latex allergy** (the needle cover on the pre-filled syringe contains a derivative of latex).
    e. **Severe renal impairment**
4. **Baseline renal function prior to initiation of denosumab.**
   Obtain patient's baseline renal function prior to initiation of denosumab.
   Confirm absence of severe renal impairment (creatine clearance is <30 ml/min). No dose adjustment is required in patients with renal impairment (SmPC). **(NB: Shared care is NOT appropriate for patients with severe renal impairment – such patients should remain under the care of the specialist.)**

5. **Calcium and vitamin D**
   Adequate intake of calcium and vitamin D is important in all patients receiving 60mg denosumab.
   - Prior to initiating therapy, the specialist should check dietary calcium intake and check vitamin D levels, Start calcium 1-1.2g plus colecalciferol 20mcg (800 IU) daily if deemed necessary, explaining the importance of taking these and the potential detriment of non-compliance
   - If adequate dietary calcium intake, then vitamin D supplementation alone may suffice.
   - Click here to view further information around dietary intake of calcium and to access a calcium intake calculator

6. **Oral Hygiene**. Specialist to assess the patient to ensure that he / she has good oral hygiene and to use clinical judgement to determine if a dental examination is required prior to initiating denosumab. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report immediately any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. Patients should be advised to contact the Specialist or their GP if they require any invasive dental procedures whilst on treatment, as these should be performed only after careful consideration and avoided close to denosumab administration. GPs should seek advice from the Specialist using 'Advice and Guidance'.
7. Discuss the benefits and possible common and uncommon **side-effects** of treatment. Please discuss the importance of notifying the doctor immediately if the patient develops a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), possibly with symptoms of fever.
8. Tell the patient to report symptoms of hypocalcaemia to their doctor (e.g., muscle spasms, twitches, or cramps, numbness or tingling in the fingers, toes, or around the mouth)
9. **Compliance**:

Ensure the patient understands the importance of compliance with denosumab treatment. Explain that it is very important that denosumab injections are given every 6 months (plus or minus 2 weeks) as any delay in treatment increases the risk of developing an osteoporotic fracture.

10. Provide patient with relevant medicine information regarding treatment.
11. Explain and encourage/support the patient to register with the "Prolong Patient Support Programme"*, which gives access to further support and includes a Prolia Reminder service, ensuring patient is reminded when their next injection is due.
12. Prior to Initiation: Secondary care specialist to inform the GP that a shared care guideline (SCG) is available and to send a copy of the SCG (also available on the BLMK Medicine management website click here) with a request to share care when assessed as suitable for GP prescribing.
13. **Initiation**: Secondary care specialist to initiate first denosumab injection and discuss the shared care arrangement with the patient and ensure he/she understands the plans for follow-up care. This should be documented in the patient's notes.
14. Administer the first dose in the hospital, monitor the patient's response, and when assessed as suitable for GP prescribing, request the sharing of care with the GP.
15. **On-going treatment**: Ensure that the GP understands the rationale for subsequent doses of denosumab to be given within two weeks either side of the 6-month time period. Secondary care to write to both the patient and their GP to notify them of the date window for the **second injection,** and to advise the GP to do blood tests **4 weeks before the next dose is due (**to check if serum adjusted calcium and vitamin D are normal and creatinine clearance is > 30 ml/min.)
16. Patients who have severe renal impairment (creatinine clearance <30ml/min) **or** who are risk of hypocalcaemia will also be required to have a blood test 2 weeks after the injection (for calcium, renal function) – **NB: -** these types of patients are not suitable for shared care, and they should remain under the care of the specialist team.
17. **Adverse Events.** Secondary care specialist to report any adverse events to the MHRA http://yellowcard.mhra.gov.uk/.
18. **Changes to treatment**. Secondary care specialist to communicate promptly with the GP (within 14 days of a patient appointment) in writing / by e-mail if treatment is changed or discontinued.
19. **Review of treatment**. Secondary care specialist to review patient at 3- 5 years to assess the need to continue treatment, or sooner if GP has concerns.

* **Prolong Patient Support Programme. To register: Direct line telephone:** 0330 808 8686 **Email:** prolong.support@nhs.net **Post:** Prolong programme, Bionical Solutions Limited, The Piazza, Mercia Marina, Findern Lane, Willington, DE65 6DW https://www.prolia.co.uk/resources-for-your-patients/prolong-patient-adherence-programme

GP Responsibilities

1. GP practice to identify and confirm who will be responsible for administering the denosumab injection i.e. the GP or nurse, and that they are familiar with the SmPC requirements for administration.
2. **Compliance with treatment**:
    - Monitor patient's compliance with denosumab treatment

- Reinforce the importance of an adequate daily intake of calcium and vitamin D and therefore compliance with any supplementation (e.g., calcium 1-1.2g plus colecalciferol 20mcg (800 IU), or Vitamin D alone) recommended by the specialist
- Click here to view further information around dietary intake of calcium and the need for supplementation and to access a calcium intake calculator

3. Explain the potential detriment from non-compliance with denosumab treatment / calcium and vitamin D supplementation.
4. If the patient fails to attend for the required routine blood tests or fails to attend for the 6 monthly injection, the GP should contact the Specialist team for advice.
5. **Oral Hygiene**. Advise all patients to maintain good oral hygiene, receive routine dental check-ups, and report immediately any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab.
6. **Dental Procedures.** Patients should be advised to contact the Specialist or their GP if they require any invasive dental procedures whilst on treatment, as these should be performed **only** after careful consideration and avoided close to denosumab administration. If an invasive dental procedure is required, the GP should contact the specialist team for advice (via Advice and Guidance).

GP to take following actions in a timely manner: -

At Month 1 (i.e., 3-4 weeks after the patient receives the first dose of denosumab**)**

7. Check if patient is enrolled with the Prolong patient support programme* (usually enrolled by the nursing staff at the hospital at 1st appointment) and ensure the patient knows to respond in a timely manner to recall for making appointments for checking of blood **4 weeks before** each injection and for administration of denosumab to ensure it is received at a six-monthly interval +/- 2 weeks.
8. Add Prolia (Denosumab 60mg) every 6 months to patient record.
9. **Ensure that any prescriptions for bisphosphonates are stopped and ensure that calcium /vitamin D tablets remain on repeat if they were advised by the specialist.**
10. Practice arrangements to be made to ensure that denosumab is stored in a vaccine refrigerator and the temperature monitored daily.
11. Practices are advised to use a robust recall system to ensure patients receive timely treatment.

At Month 5 (and then every 5 months from the date of the last injection)

Ensure patient has an appointment booked for the following **3 blood tests** in preparation for second and subsequent injections in the practice:-

12. **Adjusted calcium levels**
    If serum calcium below normal, GPs should seek specialist advice (via Advice and Guidance).

13. **25-OH vitamin D**
    IF serum vitamin D below 50nmol/L, but calcium normal, load as appropriate according to clinical guideline for management of vitamin D deficiency then recall patient for re-test at 4 weeks.
    IF levels remain below normal check compliance with therapy and seek advice on further treatment of risk factors for osteoporotic fractures.

14. **Renal function**
    If patient has severe renal impairment (creatinine clearance <30ml/min*) measured 4 weeks before next injection is due, **DO NOT GIVE** Prolia® (Denosumab 60mg) and **refe**r to hospital specialist for review.

* The Creatinine Clearance calculator in SystmOne or an online Creatinine Clearance calculator may be used to determine the patient's creatinine clearance.

NB: Patients with or who develop severe renal impairment; or those with hypocalcaemia or patients at risk of developing hypocalcaemia, are not suitable for shared care and should be referred to the Specialist team.

At Month 6 (and every 6 months from the date of the last denosumab injection)
(Treatment to be given within a one-month window around each 6-month time point (i.e., +/- 2 weeks either side of due date)

15. Check calcium and vitamin D levels and renal function are within normal range for ALL patients **before** each dose of denosumab is given.
16. Contact the Specialist for advice if a patient's blood test indicate hypocalcaemia or if the patient presents with symptoms of suspected hypocalcaemia.
17. Tell all patients to report symptoms of hypocalcaemia to their GP (e.g., muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth
18. Check calcium levels at any time if suspected signs of hypocalcaemia occur.
19. Refer any patients who develops severe renal impairment back to the specialist team.
20. Ensure patient maintains healthy diet and adequate daily intake of calcium and vitamin D, with a review of supplementation as required
21. Confirm with patient that they are aware of potential adverse reactions and to report them to the practice.
22. Check for new or unusual symptoms of hip, thigh, or groin pain. If present, consider whether evaluation is required to look for atypical femoral fracture.
23. Check for new or unusual symptoms relating to ears or jaw – see MHRA information regarding osteonecrosis of the jaw and external auditory canal (appendix 2)

Administration

24. If calcium level and renal function are normal and if no other issues, administer denosumab (Prolia ®)
25. Record Batch number administered, and injection site used in the patient's notes.
26. **NB: If denosumab is NOT able to be administered for any reason, the GP should contact the Specialist team for advice** (as per MHRA advice Aug 2020)
27. GP to make arrangements to contact the secondary care specialist if patients discontinue denosumab or are lost to follow-up.
28. GP to report any adverse events to the MHRA http://yellowcard.mhra.gov.uk/

Useful sources of information for prescriber
Prolia® Summary of Product Characteristics - http://www.medicines.org.uk/emc/medicine/23127
Prolia® Patient Information Leaflet available from pack
Prolia® Patient Information Leaflet available online. You can download a copy from http://www.medicines.org.uk/emc/PIL.23128.latest.pdf
Denosumab BNF monograph: https://bnf.nice.org.uk/drug/denosumab.html

* **Prolong Patient Support Programme ; To register: Direct line telephone:** 0330 808 8686 **Email:** prolong.support@nhs.net **Post:** Prolong programme, Bionical Solutions Limited, The Piazza, Mercia Marina, Findern Lane, Willington, DE65 6DW https://www.prolia.co.uk/resources-for-your-patients/prolong-patient-adherence-programme

Patient's Role (or that of carer)

1. Patient to notify the GP or secondary care specialist if he/she:
   - has an allergy to latex
   - has ever had severe kidney problems, kidney failure or has needed dialysis
   - has cancer, is undergoing chemotherapy or radiotherapy,
   - is taking steroids,
   - is pregnant, thinks they may be pregnant, or is planning to get pregnant. (Also, if they are breast-feeding or planning to do so.)
2. Report to the specialist or GP if patient does not have a clear understanding of the treatment.
3. Patient to immediately report any adverse events to the GP or Hospital doctor, whoever last administered denosumab, particularly if patient develops a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), symptoms of fever, muscle aches, dizziness, and any dental problems.
4. Patient to present rapidly to the GP or secondary care specialist should their condition significantly worsen, or they experience any adverse reactions.

5. Patient to inform GP:
   - If they have symptoms of hypocalcaemia (e.g., muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth)
   - Patient needs to maintain good oral hygiene – patient needs to inform GP if they do not receive routine dental care, or have gum disease.
   - Patient to tell GP and their dentist that they are receiving denosumab if currently having dental treatment or planning to undergo dental surgery,
   - if they experience ear symptoms including chronic ear infections.
6. Patient needs to ensure they are maintaining adequate calcium and vitamin D intake through a healthy diet and taking any supplements if required, as advised by the specialist / GP
7. Patient to make appropriate appointments with GP: -
   - for a blood test **4 weeks before** the next denosumab injection is due (to check calcium, renal function, and vitamin D), **AND**
   - an appointment to receive the 6 monthly injection.

Appendix 1

Denosumab (Prolia ®) -
General Clinical Information and Monitoring Requirements

The following information highlights key prescribing information, blood test monitoring requirements and MHRA alerts with regards denosumab (Prolia®). It is however not designed to be an exhaustive document. Clinicians should refer to the Summary of Product Characteristics (SmPC) and the current electronic BNF for full prescribing details with regards dosage, contraindications, side effects, drug interactions etc.

- SmPC: https://www.medicines.org.uk/emc/product/568/smpc
- BNF: www.bnf.org/products/bnf-online

Clinicians are reminded to report any suspected adverse effects via the yellow card scheme.

Licensed Indication(s):	• Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures. • Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture • Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.
Place in Therapy:	As per BLMK osteoporosis guidelines: https://medicines.blmkccg.nhs.uk/guideline/osteoporosis-guideline/ • Management of osteoporosis in post-menopausal women in primary care (both primary and secondary prevention of osteoporotic fragility fractures) (as per **NICE - TA 204)** • Management of osteoporosis in men (age ≥ 50 years) in primary care (both primary and secondary prevention of osteoporotic fragility fractures • Prevention and Treatment of glucocorticoid-induced osteoporosis in post-menopausal women **and** men (age ≥ 50 years) (in primary care)
Therapeutic summary:	Denosumab is a monoclonal antibody drug for the treatment of osteoporosis in limited circumstances.
Dose & route of administration:	Denosumab is administered as a single subcutaneous injection into the thigh, abdomen or back of the arm.

	The recommended dosage is 60 mg once every 6 months (twice a year) by sub-cutaneous injection, administered by an individual who has been adequately trained in sub-cutaneous injection technique. It is important that patients receive their 6 monthly injection in a timely manner, within 2 weeks either side of the due date. There is a potential for rebound bone loss if the injection is delayed more than this and so patients who discontinue or are lost to follow up should be alerted to the osteoporosis secondary care specialist where appropriate.
Contraindications:	• Denosumab is contraindicated in hypocalcaemia • Hypersensitivity to the active substance or to any of the excipients
Clinically relevant Precautions	**Special warnings and precautions** ***Skin infection*** Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. ***Calcium and vitamin D supplementation*** Adequate intake of calcium and vitamin D is important in all patients. **Hypocalcaemia** ***(See MHRA DSU* October 2012 and *DSU* Sept 2014) *** Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia. Monitoring of calcium and vitamin D status to be undertaken in accordance with local guidelines/practice in patients with severe renal impairment. ***Osteonecrosis of the jaw (ONJ)*** ***(See MHRA DSU Sept 14 and DSU July 2015)*** ***Sept 2014) **** ONJ has been reported in patients treated with denosumab The risk of ONJ increases with increasing duration of treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with concomitant risk factors. Whilst on treatment, these patients should avoid invasive dental procedures unless necessary.

	Good oral hygiene practices should be maintained during treatment with denosumab. For patients who develop ONJ while on denosumab therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with denosumab, refer to secondary care specialist. ***Osteonecrosis of the external auditory canal*** ***(See MHRA DSU June 2017) **** The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment. ***Atypical fractures of the femur*** ***(See MHRA DSU update Feb 2013) **** ***Stopping or delaying ongoing therapy*** *increases the risk of multiple vertebral fractures* (**See MHRA DSU update, Aug 2020) *** **Unnecessarily long-term antiresorptive treatment** (including both denosumab and bisphosphonates) without regular re-assessment / re-evaluation **Concomitant treatment** Patients should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours). **Latex/ Dry natural rubber allergy -** The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. **Excipients:** o contains 47 mg sorbitol in each mL of solution. It should not be used in patients who have a rare hereditary problem of fructose intolerance. o The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. o contains less than 1 mmol sodium (23 mg) per 60 mg that is to say essentially 'sodium-free'. *. See appendix 2 for links to MHRA DSUs

Renal Impairment	No dose adjustment is required in patients with renal impairment. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients. No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment creatinine clearance < 30 ml/min). **NB: It has been agreed locally that GPs should not prescribe denosumab for patients with severe renal impairment (see Osteoporosis guidelines[2]) and that the care of such patients should remain with the Specialist team.**
Hepatic impairment	The safety and efficacy have not been studied in this population
Elderly (≥ 65 years)	No dose adjustment is required.
Calcium and vitamin D supplementation	Adequate intake of calcium and vitamin D is important in all patients taking denosumab 60mg. All patients on treatment for osteoporosis should be prescribed calcium 1-1.2g plus colecalciferol 20mcg (800IU) daily UNLESS the clinician is confident that the patient has adequate calcium intake and is vitamin D replete.[2] (If adequate dietary calcium intake has been established, then vitamin D supplementation alone may suffice.) Click here to view further information around dietary intake of calcium and the need for supplementation and to access a calcium intake calculator
Clinically relevant drug interactions:	Interaction with other medicinal products and other forms of interaction Access up to date SPC information here.
Adverse effects	See summary of product characteristics (SmPC) for full list https://www.medicines.org.uk/emc/medicine/23127#UNDESIRABLE_EFFECTS • The most common side effects (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. • Other commonly reported side effects include UTI, upper respiratory tract infections, sciatica, cataracts, constipation, abdominal discomfort, rash, and eczema. • Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw atypical femoral fractures and osteonecrosis of the auditory ear have been observed in patients taking denosumab (Prolia®)

	NB: Tell all patients to report symptoms of hypocalcaemia to their doctor (e.g., muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).
Duration of treatment:	**Review of treatment:** o In line with MHRA advice (Aug 2020), denosumab **should not be stopped or ongoing treatment delayed without a specialist review** (due to increased risk of multiple vertebral fractures reported). o Patients should be sent for a repeat DEXA scan around the 3-5 year mark as part of the ongoing review process. Specialists will then issue advice regarding duration of treatment required on the DEXA report or alternatively they can be contacted for advice via 'Advice and Guidance'.
Preparations available (Manufacturer)	Prolia® 60 mg solution for injection in a pre-filled syringe By Amgen Limited
	NB: There is a higher strength denosumab product, XGEVA® used for the prevention of skeletal related events in adults with bone metastases from solid tumours. **This product is not suitable for osteoporosis treatment and is NOT covered by this shared care guideline.**

Monitoring

- Pre Denosumab-dose - All patients should have an adjusted calcium level, vitamin D level and renal function checked **approximately 4 weeks prior** to receiving a dose of denosumab.
- Post Denosumab dose - clinical monitoring of calcium levels 2 weeks after denosumab is recommended for patients pre-disposed to hypocalcaemia and those with severe renal impairment (creatinine clearance < 30ml/min) or receiving dialysis. (These types of patients are not suitable for shared care, and should remain under the care of the specialist team)

Timing of Interventions in relation to date of denosumab injection	**Monitoring**	**Responsible Clinician**
PRIOR TO COMMENCING SHARED CARE		
Prior to administration of first dose of denosumab	Check the following: • Adjusted serum Calcium level • 25OH Vitamin D level • Renal function NB: If patient has severe renal impairment, shared care is not appropriate, and the patient should remain under the sole care of the specialist team	**Specialist**

2 weeks post first dose	Check adjusted serum calcium level in patients who have: - • severe renal impairment • who are at risk of developing hypocalcaemia • who have suspected symptoms of hypocalcaemia	
AFTER COMMENCEMENT OF SHARED CARE		
Second dose and subsequent doses:	**Check the following bloods tests, 4 weeks before next dose of denosumab is due:** • Adjusted serum calcium level • 25OH vitamin D level • Renal function (creatine clearance) NB: If the patient has severe renal impairment (creatinine clearance* <30ml/min) measured prior to next dose of denosumab is due, they should **NOT** be given denosumab and should be referred to secondary care – **patients with severe renal impairment are no longer eligible for shared care and should remain under the care of the specialist team.** * The Creatinine Clearance calculator in SystmOne or an online Creatinine Clearance calculator may be used to determine the patient's creatinine clearance.	**GP**
Month 6 (and every 6 months from the date of the last denosumab injection)	Give a dose of Denosumab and assess for ADRs	**GP/ Nurse**
2 weeks post denosumab dose	A **post dose calcium level** is not routinely required except in the following patients: - • patients with severe renal impairment (creatinine clearance < 30ml/min) • in patients at risk of developing hypocalcaemia	**GP / Specialist / Nurse**
Treatment Review	Annual review by GP - If patient is tolerating treatment; complying with blood test monitoring; attending	GP / Specialist

	every 6 months for treatment, **and** has no additional risk factors, <u>continue</u> treatment, and send for specialist review and a repeat DEXA scan after 3-5 years of treatment. If additional risk factors are present, seek specialist advice (via Advice and Guidance) regarding suitability for continuation / need to change therapy. NB: In line with MHRA advice (Aug 2020), denosumab **should not be stopped or ongoing treatment delayed without a specialist review** (due to increased risk of multiple vertebral fractures reported).		
Practical issues: **Source of denosumab in primary care**	There are two ways in which denosumab can be sourced in primary care. **Practices are encouraged to order this themselves rather than issue an FP10.** **1)** A GP practice can have an account with AAH Pharmaceuticals Ltd, and orders can be placed by telephone or online. Denosumab (Prolia®) product code **<u>PRO2653L</u>** • AAH Customer Care telephone number: 0344 561 8899 (8:30-19:00 Mon-Fri.) • Online orders: <u>www.AAH.co.uk</u> (with your username and password) (If a GP practice is a new customer an account can be set up: Visit **aah.co.uk/s/opening-an-aah-account** and follow the steps to open an account. The AAH team will then contact you. Please note that the online application must be signed by a partner/director and AAH cannot accept the typed font option on DocuSign). If you have any further questions, please contact AAH Customer Care via Live Chat on AAH Point, or by calling 0344 561 8899. Denosumab (Prolia®) will be delivered within 24 hours via refrigerated vehicles to the premises free of charge. Stock is then held in the fridge at the surgery until required. Alternatively **2)** The patient can receive the drug from a Community Pharmacy through an FP10 written by the GP. Patients are likely to have to		

	return to the pharmacy after 2 working days to collect the injection, as most pharmacies will not stock this drug, as patient numbers will be small. Please note: Store denosumab in a pharmaceutical grade refrigerator (2˚C - 8˚C). Do not freeze. Keep the pre-filled syringe in the outer carton to protect from light. Do not shake excessively. Denosumab may be stored at room temperature (up to 25˚C) for up to 30 days in the original container. Once removed from the refrigerator, denosumab must be used within this 30 day.

Appendix 2

MHRA Drug Safety Update (DSU) Information

There have been **6 MHRA Drug Safety Updates (DSU)** relating to denosumab published to date.

Details of these are provided below. Click the links to access the relevant DSU.

1). Denosumab: fatal cases of severe hypocalcaemia- monitoring recommendations
MHRA DSU, published October 2012

- **Hypocalcaemia:** In October 2012, the MHRA issued a warning regarding the risk of hypocalcaemia with denosumab use, especially in patients with severe renal impairment or receiving dialysis.

2). Denosumab: Atypical fracture of the femur
MHRA DSU, published Feb 2013

- In Feb 2013, the MHRA issued a Drug Safety update entitled “Denosumab 60 mg (Prolia): rare cases of atypical femoral fracture with long-term use”. This update is regarding the long-term use of Denosumab 60 mg (Prolia▼) and reports of rare cases of atypical femoral fracture.

3). Denosumab: monitoring for hypocalcaemia – updated recommendations
Denosumab: Minimising the risk of osteonecrosis of the jaw
MHRA DSU, Published in Sept 2014

- In Sept 2014, the MHRA published a DSU covering two issues: monitoring for hypocalcaemia and minimising the risk of osteonecrosis of the jaw.

4). Denosumab: Further measures to minimise osteonecrosis of the jaw
Reminder cards
MHRA DSU, Published July 2015

- The MHRA have issued a further Drug Safety Update (DSU July 15) [7] to inform prescribers that patient reminder cards are being introduced for patients taking

denosumab and intravenous bisphosphonates. These cards inform patients of the risk of osteonecrosis of the jaw and precautions to take before and during treatment. These can be accessed below.

5). Denosumab: Osteonecrosis of the external auditory canal
MHRA DSU, Published June 2017

- In June 2017, the MHRA published a DSU detailing 5 reports worldwide, of osteonecrosis of the external auditory canal in patients treated with 60mg denosumab for osteoporosis. In December 2015, the MHRA published a Drug Safety Update (DSU) article about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates.

6). Denosumab: Increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment
MHRA DSU, Published August 2020

- In august 2020, the MHRA published a DSU article reporting an increased risk of multiple vertebral fractures in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis. Patient's individual benefits and risks should be evaluated before initiating therapy. Treatment for existing patients should not be stopped without specialist review.

Key references:

1. SPC. Prolia®. January 2020. Available at: https://www.medicines.org.uk/emc/medicine/23127 viewed 29-10-2020
2. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Published date: 27 October 2010 Available at: https://www.nice.org.uk/guidance/ta204 viewed 29-10-2020
3. MHRA Drug Safety Update. Denosumab: monitoring recommended. October 2012; Available at: https://www.gov.uk/drug-safety-update/denosumab-monitoring-recommended Accessed <15.05.17>
4. MHRA Drug Safety Update. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk. July 2015; Available at: https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk viewed 29-10-2020
5. MHRA Drug Safety Update: Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/620777/DSU-June_PDF.pdf viewed 29-10-2020
6. MHRA Drug Safety Update: Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment https://www.gov.uk/drug-safety-update/denosumab-60mg-prolia-increased-risk-of-multiple-vertebral-fractures-after-stopping-or-delaying-ongoing-treatment
7. NICE BNF Denosumab https://bnf.nice.org.uk/drug/denosumab.html#indicationsAndDoses viewed 29-10-2020

Document History

MK shared care guideline - Approved by (date approved): Milton Keynes Prescribing Advisory Group – MKPAG (November 2020)
Original Authors: Dr. Anne Jenkins and Debbie Morrison
Review Author: 2017: This updated guidance has been reproduced by Dupe Fagbenro, Principal Pharmacist, Formulary Services and Prescribing Advisory Lead in collaboration Dr Anne Jenkins. It has been subject to consultation and endorsement by MKPAG. 2020 November: Reviewed and updated by Trevor Jenkins, Senior Pharmacist, MKUH. Sept 2021 Updated version written as part of the BLMK alignment process
Date Approved: BLMK wide shared care guideline – Updated Sept 2021, Sept 2022 by Medicine Optimisation team and Approved by BLMK Area Prescribing committee, Formulary Subcommittee, Sept 2022, minor amendment Nov 2022 **Review Date**: Sept 2025

Shared Care Guideline: Denosumab Prescribing Agreement
(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)

Section A: To be completed by the hospital consultant initiating the treatment

GP Practice Details: Name: …… Address: …… Tel no: …… Fax no: …… NHS.net e-mail: ……	**Patient Details:** Name: …… Address: …… DOB: ……/……/…… Hospital number: …… NHS number (10 digits): ……

Consultant name: ……..; **Clinic name:** ……..
Contact details:
Address: .....
Tel no: …… NHS.net e-mail: ……

Diagnosis: Osteoporosis	**Drug name & dose to be prescribed by GP:** Denosumab (Prolia®) 60 mg, administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm..

Next hospital appointment: ……/……/……..

Dear Dr. ……..,

Your patient was seen on …../…../……and I have started Denosumab injection for the above diagnosis.
Denosumab is to be administered as a single subcutaneous injection into the thigh, abdomen or back of the arm. The recommended dosage is 60 mg once every 6 months (twice a year). It is important that patients receive their 6 monthly injection in a timely manner, within 2 weeks of the due date either side.
The date the patient received their first injection was: ……;
The next injection is due on …….

I am requesting your agreement to sharing the care of this patient from …../…../…….. in accordance with the (attached) Shared Care Guideline.
Please take particular note of Section 2 where the areas of responsibilities for the consultant, GP and patient for this shared care arrangement are detailed.

Patient information has been given outlining potential aims and side effects of this treatment.

The patient has given me consent to treatment under a shared care prescribing agreement (with your agreement) and has agreed to comply with instructions and follow up requirements.

Letter has been sent to GP, copied to patient, with date of first injection and results of baseline tests. Please carry out further monitoring as detailed on page 7.

Thank you and kind regards

Consultant Signature: ……Date: ……/……/……....

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above

Please sign and return your agreement to shared care within 14 days of receiving this request
Tick which applies:

□ I accept sharing care as per shared care prescribing guideline and above instructions

□ I would like further information. Please contact me on:…….

□ I am not willing to undertake shared care for this patient for the following reason:

…….

GP name: ……..…….

GP signature: …… Date: …/…/…..

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)